DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

Pilot Training and Research Program; Demonstration Project; Studies in Clinical Pharmacology and New Drug Review Technologies; Availability of Cooperative Agreements; Request for Applications

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA), Center for Drug Evaluation and Research (CDER) is announcing the anticipated availability of funds for training and research cooperative agreements for fiscal year (FY) 2000. This pilot program is a demonstration project to evaluate the extent to which such a program can contribute to an identifiable increase in the number of trained biomedical, scientific personnel in clinical pharmacology. Research will be conducted to study clinical pharmacology and biopharmaceutics issues related to new drug development and review. If funds are appropriated in FY 2000 for the program, FDA anticipates that approximately $3.0 million will be available. FDA anticipates making 4 to 10 cooperative agreement awards to domestic medical schools at $300,000 to $750,000 per award per year (direct and indirect costs). Support for these agreements may be for up to 3 years. The number of agreements funded will depend on the quality of the applications received and the availability of Federal funds to support the projects.

DATES: Submit applications by (*insert date 30 days after date of publication in the* **Federal Register**). If the closing date falls on a weekend, it will be extended to Monday; if the date falls on a holiday, it will be extended to the following workday.

ADDRESSES: Application forms are available from, and completed applications should only be submitted to: Rosemary Springer, Senior Grants Management Specialist (HFA–520), Food and Drug

Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–827–7182. Applications hand-carried or commercially delivered should be addressed to 5630 Fishers Lane, rm. 2129, Rockville, MD 20852. Application forms can also be found at ''http://www.nih.gov/grants/phs398/forms-toc.html''.

FOR FURTHER INFORMATION CONTACT:

Regarding the administrative and financial management aspects of this notice: Rosemary Springer (address above).

Regarding the programmatic aspects of this notice: Shiew-Mei Huang, Office of Clinical Pharmacology and Biopharmaceutics, Center for Drug Evaluation and Research (HFD–850), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–594–5690.

SUPPLEMENTARY INFORMATION: FDA, CDER is announcing the anticipated availability of funds for FY 2000 for awarding cooperative agreements to support post-doctoral training of clinical pharmacologists. The training to be supported will be research studies related to new drug development and review. FDA will support the studies covered by this notice under Public Law 102–222. The law authorizes a pilot program for training additional clinical pharmacologists. If funding is available, FDA will award Demonstration Cooperative Agreements to evaluate the extent to which such a program can contribute to increasing the number of trained biomedical, scientific personnel in clinical pharmacology. FDA's extramural program is described in the Catalog of Federal Domestic Assistance, No. 93.948.

The Public Health Service (PHS) strongly encourages all award recipients to provide a smoke-free work place and to discourage the use of all tobacco products. This is consistent with the PHS mission to protect and advance the physical and mental health of the American people. PHS urges applicants to submit work plans that address specific objectives of ''Healthy People 2000.'' Potential applicants may obtain a copy of Healthy People 2000 (Full Report, stock No. 017–00100474–0) through the Superintendent of Documents, Government Printing Office, Washington, DC 20402–9325, 202–512–1800.

PHS Policy is that applicants for PHS clinical research grants are required to include minorities and women in study populations so that research findings can be of benefit to all persons at risk of the disease, disorder or condition under study; special emphasis must be placed on the need for inclusion of minorities and women in studies of diseases, disorders, and conditions which disproportionately affect them. This policy is intended to apply to males and females of all ages. If women or minorities are excluded or inadequately represented in clinical research, particularly in proposed population-based studies, a clear and compelling rationale must be provided.

Some activities carried out by a recipient under this announcement may be governed by Department of Health and Human Services' regulations for the protection of human research subjects (45 CFR part 46). These regulations require recipients to establish procedures for the protection of subjects involved in any research activities. Prior to funding and upon request of the Office for Protection from Research Risks (OPRR), prospective recipients must have on file with OPRR an assurance to comply with 45 CFR part 46. This assurance to comply is called an Assurance document. It includes the Institutional Review Board (IRB) designated for review and approval of procedures for carrying out any research activities occurring in conjunction with this award. If an applicable Assurance document for the applicant is not already on file with OPRR, a formal request for the required Assurance will be issued by OPRR at an appropriate point in the review process, prior to award, and examples of required materials will be supplied at that time. No applicant or performance site, without an approved and applicable Assurance on file with OPRR, may spend funds on human subject activities or accrue subjects. No performance site, even with an OPRR-approved and applicable Assurance, may proceed without approval by OPRR of an applicable Assurance for the recipients. Applicants may wish to contact OPRR by facsimile 301–402–0527 to obtain preliminary guidance on human subjects' issues. When contacting OPRR, applicants should provide their institutional affiliation, geographic location, and all available Requests for Application (RFA) citation information.

Applicants are advised that the section on human subjects on pages 7 and 8 in the application kit entitled ''Section C. Specific Instructions—Forms, Item 4, Human Subjects,'' should be carefully reviewed for the certification of Institutional Review Board (IRB) approval requirements. Documentation of IRB approval for every participating center is required to be on file with the Grants Management Officer, FDA. The goal should be to include enough information on the protection of human subjects in a sufficiently clear fashion so reviewers will have adequate material to make a complete review.

Consent and/or assent forms, and any additional information to be given to a subject, should accompany the grant application. Information that is given to the subject or the subject's representative must be in language that the subject or his or her representative can understand. No informed consent, whether oral or written, may include any language through which the subject or the subject's representative is made to waive any of the subject's legal rights, or by which the subject or representative releases or appears to release the investigator, the sponsor, or the institution or its agent from liability. If a study involves both adults and children, separate consent forms should be provided for the adults and the parents or guardians of the children.

The elements of informed consent are stated in the regulations at 45 CFR 46.116 and 21 CFR 50.25 as follows:

1. Basic elements of informed consent.

In seeking informed consent, the following information shall be provided to each subject.

(a) A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental.

(b) A description of any reasonably foreseeable risks or discomforts to the subject.

(c) A description of any benefits to the subject or to others which may reasonably be expected from the research.

(d) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.

(e) A statement that describes the extent, if any, to which confidentiality of records identifying the subject will be maintained, and that notes the possibility that FDA may inspect the records.

(f) For research involving more than minimal risk, an explanation as to whether any compensation and any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained. Additional protections for children involved as subjects in research are found in 45 CFR part 46, subpart D.

(g) An explanation of whom to contact for answers to pertinent questions about the research and research subject's rights, and whom to contact in the event of research-related injury to the subject.

(h) A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

2. Additional elements of informed consent.

When appropriate, one or more of the following elements of information shall also be provided to each subject.

(a) A statement that the particular treatment or procedure may involve risks to the subject (or the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable.

(b) Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent.

(c) Any costs to the subject that may result from participation in the research.

(d) The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.

(e) A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject.

(f) The approximate number of subjects involved in the study.

Additional protections for children involved as subjects in research are found in 45 CFR part 46, subpart D.

The informed consent requirements are not intended to preempt any applicable Federal, State, or local laws which require additional information to be disclosed for informed consent to be legally effective.

Nothing in the notice is intended to limit the authority of a physician to provide emergency medical care to the extent that a physician is permitted to do so under applicable Federal, State, or local law.

I. Background

There is currently a nationwide shortage of trained clinical pharmacologists at a time when advances in molecular medicine have provided an unparalleled opportunity to better understand pharmacotherapeutics. This shortage limits the number of clinical pharmacologists trained in the range of new technologies that are driving the future directions of drug development and regulatory science. Clinical pharmacologists have tremendous potential to translate molecular insights and technology in a way that would promote the public health, improve the quality and speed of the regulatory review, and accelerate the development of new drugs in this country. Public Law 102–222 authorizes a pilot project for a modern training program to increase clinical pharmacology and mechanistic knowledge in this country, and to help alleviate this shortage of trained biomedical personnel. With this authority and appropriated funding, FDA will establish a Demonstration Project to evaluate whether training and research cooperative agreements can contribute to an increase in the number of trained clinical pharmacologists. The public health role of the FDA's CDER in this program relates directly to the safe and effective use of prescription drugs. Several areas

of clinical pharmacology and biopharmaceutics research are related to the public health by providing a bridge between bedside observations of clinical outcome, and molecular insights and mechanistic knowledge. FDA seeks to have research conducted in the clinical pharmacology training program that will develop:

1. Understanding of the multiple enzyme isoforms responsible for drug-drug interactions and the variations in risk associated with different metabolic pathways;

2. The application of pharmacogenomics to characterize the mechanisms of disease to target drug therapies to the causative events and pathways of disease progression;

3. The development of molecularly based biological markers and surrogate endpoints for clinical outcomes that can be linked to systemic drug exposure to provide ways to assess early treatment interventions and long term management of chronic diseases;

4. The application of sophisticated mechanistic-based exposure-response models to design human clinical trials and simulate clinical outcomes as a function of drug input and patient variables;

5. The development of an electronic bioinformatic database to manage key metabolic and drug-drug interaction data that can provide the core knowledge for an expert system intended to predict clinical risks from in vitro and in vivo data; and

6. The biopharmaceutics and clinical pharmacology characterization of complex drug substances including botanicals, herbs, and endogenous proteins to offer the possibility that these agents can be used more effectively and safely in the early treatment and long-term management of diseases.

II. Research Goals and Objectives

The specific objective of this training and research program will be to provide financial assistance to investigators who conduct research as part of their clinical pharmacology training program. It is of particular importance to the public health that this program advance scientific knowledge of mechanisms of in vitro/in vivo metabolism/drug interactions; characterization of

individual exposure-response to drugs; and the effect of age, gender, and race on drug disposition and exposure-response relationships. Projects that fulfill any one or a combination of the following specific objectives will be considered for funding:

1. Mechanistic understanding of drug-drug, drug-food (e.g., grapefruit juice), and drug-non-prescription product interactions in the general population;

2. Research to understand the mechanistic basis for individual variability in pharmacokinetics and pharmacodynamics as a function of intrinsic (gender, age) and extrinsic (co-administered drugs) factors: application of pharmacogenomics, pharmacogenetics biological markers, and surrogate endpoints to link exposure to clinical outcome;

3. Research to develop and evaluate biomarkers, and evaluate noninvasive imaging as a way to assess safety and efficacy;

4. Computer modeling and clinical trial simulations: evaluation of clinical study designs to confirm drug safety and efficacy; evaluation of these techniques in the assessment of gender-, age-,

race-, and liver/kidney function-specific differences in drug response and drug interactions;

5. Development of electronic databases to capture key metabolism/drug interaction data and provide a linkage to an expert system to assist new drug application reviews of pre-clinical and clinical drug interaction data; and

6. Research to define the clinical pharmacology characteristics (such as dose-exposure-response) of complex drug substances (such as conjugated estrogens, botanical, and proteins), to assure proper use of these substances; research to define the biopharmaceutic characteristics of the active ingredients for these substances and development of ways to establish the equivalency of these dosage forms to establish standards for new and generic product approvals.

III. Reporting Requirements

A Program Progress Report and an annual Financial Status Report (FSR) (SF–269) are required under 45 CFR 74.51 and 74.52. An original FSR and two copies shall be submitted to FDA's

Grants Management Officer within 90 days of the budget expiration date of the cooperative agreement. Failure to file the FSR (SF–269) on time will be grounds for suspension or termination of the grant. Progress reports will be required semiannually. The first report will be due 6 months after award and the second report that will also serve as the annual report will be due 90 days after the budget expiration date. CDER program staff will advise the recipient of the suggested format for the Program Progress Report at the appropriate time. A final FSR (SF–269) and Program Progress Report must be submitted within 90 days after the expiration of the project period as noted on the Notice of Grant Award.

Program monitoring of recipients will be conducted on an ongoing basis and written reports will be reviewed and evaluated at least semiannually by the Project Officer. Project monitoring may also be in the form of telephone conversations between the Project Officer/Grants Management Specialist and the Principal Investigator and/or a site visit with appropriate officials of the recipient organization. The results of these monitoring activities will be duly recorded in the official file and may be available to the recipient upon request.

IV. Mechanism of Support

A. Award Instrument

Support for this program will be in the form of demonstration cooperative agreements. These demonstration cooperative agreements will be subject to all policies and requirements that govern the research grant programs of the Public Health Service, as modified by this RFA, including the provisions of 42 CFR part 52 and 45 CFR parts 74 and 92. The regulations issued under Executive Order 12372 do not apply to this program.

B. Eligibility

These demonstration cooperative agreements are available to any domestic public or private medical school. For-profit entities must commit to excluding fees or profit in their request for

support to receive awards. Organizations described in section 501(c)(4) of the Internal Revenue Code of 1968 that engage in lobbying are not eligible to receive awards.

C. Length of Support

The length of support will be for up to three years. Funding beyond the first year will be noncompetitive and will depend upon: (1) Satisfactory performance during the preceding year; and (2) the availability of Federal fiscal year appropriations.

V. Delineation of Substantive Involvement

Inherent in the cooperative agreement award is substantive involvement by the awarding agency. Accordingly, FDA will have substantive involvement in the programmatic activities of all the projects funded under this RFA. Substantive involvement includes, but is not limited to, the following:

1. FDA will appoint Project Officers who will actively monitor the FDA supported program under each award and collaborate with award recipients;

2. FDA will review experimental protocols describing study objectives, study design, and data analysis methods prepared by Award recipients;

3. FDA Project Officers and scientists will collaborate with the recipient and have final approval on the experimental protocol;

4. FDA will collaborate on the interpretation of findings and may incorporate information from studies in agency policy decisions benefiting the public health;

5. FDA Project Officers will be eligible to participate as coauthors on publications based on the research conducted.

VI. Review Procedure and Criteria

A. Review Method

Grants management and program staff will first review all applications submitted in response to this RFA for responsiveness to the RFA. If applications are found to be nonresponsive, they will be returned to the applicant without further consideration.

Responsive applications will be reviewed and evaluated for scientific and technical merit by an ad hoc panel of experts in the subject field of the specific application. Responsive applications will also be subject to a second level of review by a National Advisory Council for concurrence with the recommendations made by the first level reviewers, and the final funding decisions will be made by the Commissioner of FDA or designee.

B. Program Review Criteria

Applicants are strongly encouraged to contact FDA to resolve any questions regarding criteria or administrative procedure prior to the submission of their application. All questions of a technical or scientific nature must be directed to the CDER contact and all questions of an administrative or financial nature must be directed to the Grants Management Office. (See the "**FOR FURTHER INFORMATION CONTACT**" section at the beginning of this document.) Responsiveness will be based on the following criteria:

1. Post-doctoral training and research studies should be proposed on one or more of the six clinical pharmacology and biopharmaceutics objectives listed in this notice under section II: Research Goals and Objectives;

2. Whether the proposed study is within the budget and costs have been adequately justified and fully documented;

3. Soundness of the rationale for the proposed study and appropriateness of the study design to address the objectives of the RFA;

4. Availability and adequacy of laboratory and associated clinical pharmacology and biopharmaceutics resources;

5. Availability and adequacy of support services, e.g., biostatistics, computers, etc.; and

6. Research experience, training, and competence of the Principal Investigator and support staff.

VII. Submission Requirements

Applications must contain one or more of the research objectives in section II of this notice but may also contain other objectives not specifically identified. However, each objective must be described and budgeted independently. An overall budget incorporating all objectives must be submitted as reflected on pages DD and EE of the Grant Application Form PHS 398 (rev. 5/ 95).

Budget items normally allowed under Federal research programs will be considered allowable under this program. In addition, stipend support may be requested. Stipend levels may not exceed those which are allowed under NIH regulations. Applicants may refer to the NIH web site ''http:/ /www.nih.gov/grants/guide/notice.files/not98–161.html'' for current stipend levels. PHS funds can be used for stipends paid only to a U.S. citizen, a noncitizen national, or a person who has been lawfully admitted to the U.S. for permanent residence at the time of the application. Payback requirements are not applicable under this program. PHS Expanded Authorities do not apply. Indirect costs requested may not exceed 8 percent and will exclude equipment in the base.

The original and five copies of the completed Grant Application Form PHS 398 (Rev. 5/ 95) with copies of the appendices for each of the copies, must be delivered to Rosemary Springer (address above). Submit applications by (*insert date 30 days after date of publication in the* **Federal Register**). If the closing date falls on a weekend, it will be extended to Monday; if the date falls on a holiday, it will be extended to the following workday. No supplemental or addendum material will be accepted after the receipt date.

The outside of the mailing package and item 2 of the application face page should be labeled, ''Response to RFA FDA CDER–CP–2000.''

VIII. Method of Application

A. Submission Instructions

Applications will be accepted during normal working hours, 8 a.m. to 4:30 p.m., Monday through Friday, on or before the established receipt date. Applications will be considered received on time if sent or mailed on or before the receipt date as evidenced by a legible U.S. Postal Service dated postmark or a legible date receipt from a commercial carrier, unless they arrive too late for orderly processing. Private metered postmarks shall not be acceptable as proof of timely mailing. Applications not received on time will not be considered for review and will be returned to the applicant. (Applicants should note that the U.S. Postal Service does not uniformly provide dated postmarks. Before relying on this method, applicants should check with their local post office.)

Do not send applications to the Center for Scientific Research (CSR), National Institutes of Health (NIH). Any application that is sent to the NIH and therefore not received in time for orderly processing, will be deemed unresponsive and returned to the applicant. Instructions for completing the application forms can be found on the NIH home page on the Internet (address ''http://www.nih.gov/grants/phs398/phs398.html''; the forms can be found at ''http://www.nih.gov/grants/phs398/forms—toc.html''). However, as noted above, applications are not to be mailed to the NIH. (Applicants are advised that FDA does not adhere to the page limitations or the type size and line spacing requirements imposed by the NIH on its applications). Applications must be submitted via mail delivery as stated above. FDA is unable to receive applications electronically. The Institutional National Research Service Award requirements do not apply.

B. Format for Application

Submission of the application must be on Grant Application Form PHS 398 (Rev. 5/95). All ''General Instructions'' and ''Specific Instructions'' in the application kit should be followed with the exception of the receipt dates and the mailing label address. Do not send applications to the CSR, NIH.

The face page of the application should reflect the request for applications number RFA–FDA–CDER–CP–2000.

C. Confidentiality of Information

Data included in the application, if restricted with the legend specified below, may be entitled to confidential treatment as trade secret or confidential commercial information within the meaning of the Freedom of Information Act (5 U.S.C. 552(b)(4)) and FDA's implementing regulations (21 CFR 20.61).

Legend: Unless disclosure is required by the Freedom of Information Act as amended (5 U.S.C. 552) as determined by the freedom of information officials of the Department of Health and Human Services or by a court, data contained in the portions of this application which have been specifically identified by page number, paragraph, etc., by the applicant as containing restricted information shall not be used or disclosed except for evaluation purposes.

IX. Paperwork Reduction Act of 1995

In compliance with the Paperwork Reduction Act of 1995 (44 U.S.C. 3501–3520), the Office of Management and Budget (OMB) has assigned OMB control number 0925–0001 to the collection of information regarding grant applications in Form PHS 398. This approval expires February 28, 2001.

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Dated: July 2, 1999

July 2, 1999

William K. Hubbard
Senior Associate Commissioner for
Policy, Planning and Legislation

[FR Doc. 99–???? Filed ??–??–99; 8:45 am]

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Michael W. Bell